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(21) International Application Number: PCT/US97/03110 (22) International Filing Date: 28 February 1997 (28.02.97) (30) Priority Data: 60/013,290 12 March 1996 (12.03.96) US (71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors: KUCZYNSKI, Anthony, L.; 777 West Middlefield Road #157, Mountain View, CA 94043 (US). CHILDERS, Jerry, D.; 1313 Socorro Avenue, Sunnyvale, CA 94089 (US). BARCLAY, Glen, E.; Unit C, 441 Mariposa Avenue, Mountain View, CA 94041 (US). ROGRIGUEZ, Susan; 816 Lathrop Drive, Stanford, CA 94305 (US). MERRILL, Sonya; 5002 Paseo Olivos, San Jose, CA 95130 (US). (74) Agents: SABATINE, Paul, L. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: COMPOSITION AND DOSAGE FORM COMPRISING OPIOID ANTAGONIST (57) Abstract <p>A composition of matter is disclosed and claimed comprising an opioid antagonist and a high molecular weight poly(alkylene) or a poly(carboxymethylcellulose). A dosage form is disclosed and claimed comprising the composition of matter for displacing an opioid analgesic from the dosage form.</p>		

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1 **COMPOSITION AND DOSAGE FORM COMPRISING**
2 **OPIOID ANTAGONIST**

3
4 **FIELD OF THE INVENTION**

5
6 This invention pertains to a novel composition comprising an opioid
7 antagonist. This invention also concerns a novel dosage form comprising an
8 opioid antagonist. The invention further concerns a method of administering
9 a dosage form comprising an opioid antagonist for lessening the incidence of
10 drug abuse.

11
12 **BACKGROUND OF THE INVENTION**

13
14 Analgesics are drugs which relieve pain and they act to relieve pain by
15 elevating the pain threshold of a patient in need of pain relief. One group of
16 analgesic drugs are the opiates. The opiate group of analgesics are among
17 the most powerfully acting and clinically useful drugs for the relief of pain.
18 The term opiate was once used to designate analgesic drugs derived from
19 opium including morphine, codeine and synthetic congeners of morphine.
20 With the development of totally synthetic drugs with morphine-like actions,
21 the word opioid is used to refer to all drugs, both natural and synthetic,
22 with morphine-like actions. The term narcotic as associated with the opioids,
23 refers to the physical dependence accompanying the use of these drugs and
24 with their increasing use it refers to opioid substances that cause
25 dependence.

26 In addition to their many important medical uses, the opioid drugs are
27 employed commonly for illicit purposes, including emotional, psychological,
28 euphoric, hallucinogenic, depressive, and psychedelic experiences. These
29 purposes and the physical dependence accompanying the administration of
30 these drugs has led to drug abuse. Drug abuse has become for many

1 habituates a way of life. To a rapidly growing segment of the world
2 population, use of these drugs is a vogue often seen as fashionable.
3 While these drugs are a necessary part of modern medicine, it would be
4 highly desirable to provide a novel drug delivery system and a novel
5 composition of matter that do not possess drug abuse potential, and thereby
6 seek to lessen the incidence of their abuse and their illicit use.

7

8 SUMMARY OF THE INVENTION

9

10 In view of the foregoing, it is apparent that a pressing need exists for
11 an improved delivery of opioids for their therapeutic effects, while
12 concomitantly substantially lessening or substantially preventing opioid
13 abuse. Thus, it is an object of this invention to provide a composition of
14 matter indicated for use in a dosage form comprising an abusable opioid,
15 which composition imparts a low potential for abuse of both the composition
16 and the dosage form comprising same. Another object of the invention is to
17 provide a dosage form comprising a first composition containing an opioid
18 and a second composition separate and distinct from the first composition
19 containing an antagonist for lessening opioid abuse.

20

21 DETAILED DESCRIPTION OF THE INVENTION

22

23 The term opioid as used for the purpose of this invention represents an
24 opioid member selected from the group consisting of alfentanil, allylprodine,
25 alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine,
26 bezitramide, buprenorphine, butophanol, clonitazene, codeine, cyclorphan,
27 cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide,
28 dihydrocodeine, dehydromorphine, diminoxadol, eptazocine, ethylmorphine,
29 fentanyl, hydrocodone, hydroxymethylmorphian, hydromorphone,
30 hydroxypethidine, levophenacymorphan, levorphanol, lofentanil,

1 methylmorphine, morphine, necomorphine, normethadone, normorphine,
2 opium, oxycodone, oxymorphone, pholcodine, profadol, and sufentanil.
3 The opioid can be present as a member selected from the opioid base and
4 the opioid pharmaceutically acceptable salt. The pharmaceutically
5 acceptable salt embraces the inorganic and the organic salt. Representative
6 salts include a member selected from the group consisting of hydrobromide,
7 hydrochloride, mucate, succinate, n-oxide, sulfate, malonate, acetate,
8 phosphate dibasic, phosphate monobasic, acetate trihydrate,
9 bi(heptafluorobutyrate), maleate, bi(methylcarbamate),
10 bi(pentafluoropropionate), mesylate, bi(pyridine-3-carboxylate),
11 bi(trifluoroacetate), bitartrate, chlorhydrate, fumarate, and sulfate
12 pentahydrate. The dose of opioid, in the first or opioid composition,
13 is 75 ng to 750 mg.

14 The antagonist present in the second, or antagonist composition, is an
15 effective amount to attenuate, that is to lessen and/or reduce the effect of the
16 opioid present in the first composition. The antagonist is present in 10 ng to
17 275 mg, or 0.75 to 10 wt%, in the second or antagonist composition that is
18 separate and distinct from the first or opioid composition. The antagonist is
19 an opioid antagonist selected from the group consisting of naltrexone,
20 naloxone, nalmeferone, nalide, nalmexone, nalorphine, nalpuphine, nalorphine
21 dinicotinate, and the pharmaceutically acceptable base, the pharmaceutically
22 acceptable salt thereof. The pharmaceutically acceptable addition salt
23 embraces those presented earlier in the specification.

MODES OF PERFORMING THE INVENTION

EXAMPLE 1

A novel dosage form for delivering hydrocodone to a patient in need of pain relief is prepared as follows: first, 24.8g of hydrocodone bitartrate hemipentahydrate, 70.3g of poly(ethylene oxide) of 200,000 average number molecular weight, available from Union Carbide Institute, West Virginia, and 5.0 mg of hydroxypropylmethylcellulose possessing a 11,200 average number molecular weight available from Dow Chemical Co., Midland, Michigan, are dry blended for 5 minutes using a roll mill. Then, 50 ml of denatured ethyl alcohol are added to the dry blend, and slowly mixed together for 5 minutes. After drying at room temperature, the mass is pressed through a 0.0331 inch (0.85 mm) screen, and then dried further at room temperature overnight. Next, 0.5 mg of magnesium stearate is blended with the granulation for 2 minutes to produce a homogenous blend.

Next, a second or antagonist composition is prepared as follows: first, 30.8g of poly(ethylene oxide) of 7,000,000 number average molecular weight, 15.0g of sodium chloride, and 3.0g of hydroxypropylmethylcellulose of 11,200 number average molecular weight, and 0.4g of naloxone, and 1.0g of ferric oxide are blended homogeneously in the presence of denatured alcohol. The homogenous mass is pressed through a 0.0469 inch (1.19 mm) screen and dried overnight at room temperature, and then pressed through a 0.0331 inch (0.85 mm) screen. Then, 1.0 mg of lubricant is added to the granulation. Then, 450 mg of the first composition and 250 mg of the second composition are pressed in a standard tablet press into a bilayer core with the first composition and the second composition in bilayered arrangement. The bilayered core comprises an oval shape 0.700 inches (1.78 cm) by 0.375 inches (0.95 cm).

1 The bilayered core is coated with a semipermeable membrane
2 consisting of 40 mg of cellulose acetate of 39.8% acetyl and 2 mg of
3 polyethylene glycol 3350. The membrane-forming composition is dissolved
4 in acetone:water (95:5 wt:wt), and the wall-forming composition is sprayed
5 around the bilayered core in a coater. Next, two 30 mil (0.762 mm) exit
6 passageways are drilled through the semipermeable membrane to connect
7 the opioid drug layer with the exterior of the dosage form. Finally, the dosage
8 form is dried for 48 hours at 50° to remove excess moisture.

10 EXAMPLE 2

12 A dosage form is provided by the invention by first preparing a
13 morphine composition wherein 17.28g of morphine sulfate pentahydrate,
14 38.52g of poly(ethylene oxide) possessing a 200,000 number-average
15 molecular weight, and 3.60g of poly(vinyl pyrrolidone) having a number-
16 average molecular weight of 40,000 available from ISP Technologies,
17 Texas City, Texas, are added to a planetary mixing bowl. Next, the dry
18 materials are mixed for 10 minutes. Then, 16g of denatured anhydrous
19 ethyl alcohol is slowly added to the blended materials with continuous mixing
20 for 15 minutes. Then, the freshly prepared wet granulation is passed through
21 a 20 mesh screen (0.841 mm sieve opening) allowed to dry at room
22 temperature for 20 hours and then is passed through a 16 mesh screen
23 (1.00 mm sieve opening). Next, the granulation is transferred to a planetary
24 mixer, mixed and lubricated with 0.6g of magnesium stearate.

25 Next, a push composition is prepared as follows: first, a binder
26 solution is prepared by dissolving 3g of hydroxypropylmethylcellulose
27 possessing a number-average molecular weight of 11,200 in 33.7g of water.
28 Next 0.1g of butylated hydroxytoluene is dissolved in 2g of denatured
29 anhydrous alcohol. Approximately 5g of the
30 hydroxypropylmethylcellulose/water solution is added to the butylated

1 hydroxytoluene/alcohol solution with continuous mixing for 2 to 3 minutes.
2 Next, the binder solution preparation is completed by adding the remaining
3 hydroxypropylmethylcellulose/water solution to the butylated
4 hydroxytoluene/alcohol solution, again with continuous mixing thereof.
5 Next, 36g of osmagent sodium chloride is sized using a Quadro
6 Co-mil® mill, to reduce the particle size of the sodium chloride. Next, 1.2g
7 of ferric oxide is passed through a 40 mesh screen (0.387 mm opening).
8 Then, all the screened materials and 1.2g of naloxone are added to 75.2g
9 of pharmaceutically acceptable poly(ethylene oxide) comprising a 7,000,000
10 number-average molecular weight and to 3g of hydroxypropylmethylcellulose
11 comprising a number-average molecular weight of 11,200 in a fluid bed
12 granular bowl, and the granulation process is initiated to effect granulation.
13 Next, the dry powders are air suspended and mixed for 3 minutes.
14 Then, all the binder solution is sprayed from 3 nozzles onto the
15 powder. The granulating conditions are monitored during the process.
16 Then, a fluid air mill is used to size the coated granules with an 8 mesh
17 screen (2.38 mm opening screen) and lubricated with 0.28g of magnesium
18 stearate.
19 Next, the morphine sulfate pentahydrate composition and the
20 displacement antagonist composition are compressed into a bilayer tablet.
21 First, 434 mg of the morphine sulfate pentahydrate composition is added to
22 the die cavity and compressed, then, 260 mg of the displacement antagonist
23 composition is added and the layers pressed under a pressure of
24 approximately 3 tons into a 0.700 inch (1.78cm) x 0.375 inch (0.95 cm)
25 contacting bilayer core with the antagonist separate from the opioid.
26 The bilayered core arrangement is coated with a semipermeable wall.
27 The wall forming composition comprises 95% cellulose acetate having a
28 39.8% acetyl content, and 5% polyethylene glycol having a 3350 number-
29 average molecular weight. The semipermeable wall-forming composition is
30 dissolved in an acetone:water (95:5 wt:wt) cosolvent to make a 4% solids

1 solution. The wall-forming composition is sprayed onto and around the
2 bilayer tablets in a coater. Next, two 30 mil (0.762 mm) exit passageways are
3 drilled through the semipermeable wall to connect the opioid-drug layer with
4 the exterior of the dosage system. The residual solvent is removed by drying
5 for 48 hours at 50°C and 50° humidity. The osmotic dosage forms are dried
6 further for 4 hours to 50°C to remove the excess moisture. The dosage form
7 produced by this manufacture comprises in the first composition 28.8%
8 morphine sulfate pentahydrate, 64.2% poly(ethylene oxide) possessing a
9 200,000 molecular weight, 6% poly(vinyl pyrrolidone) possessing a 40,000
10 molecular weight, and 1% magnesium stearate. The second composition
11 comprises 62.895% poly(ethylene oxide) comprising a 7,000,000 molecular
12 weight, 30% sodium chloride, 5% hydroxypropylmethylcellulose of 11,200
13 molecular weight, 0.78% antagonist naloxone, 1% ferric oxide, 0.075
14 butylated hydroxytoluene, and 0.25% magnesium stearate. The
15 semipermeable wall comprises 95% cellulose acetate comprising a 39.8%
16 acetyl content and 5.0 wt polyethylene glycol of 3350 molecular weight.
17 The dosage form comprises two passageways, 30 mil (0.762 mm) and it has
18 a morphine sulfate mean release rate of 5mg/hr.

19

20

EXAMPLE 3

21

22 A dosage form prepared according to the above example is
23 manufactured and further comprises a wall of 60 wt% to 100 wt% of a
24 cellulose polymer which polymer comprises a member selected from the
25 group consisting of a cellulose ester, cellulose diester, cellulose triester,
26 cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate,
27 cellulose triacetate, cellulose acetate, cellulose diacetate, cellulose triacetate,
28 cellulose acetate butyrate, and the like. The wall can also comprise from
29 0 wt% to 40 wt% of a cellulose ether member selected from the group
30 consisting of hydroxypropylcellulose, hydroxypropylbutylcellulose, and

1 hydroxypropylmethylcellulose and from 0 wt% to 20 wt% of polyethylene
2 glycol. The total amount of all components comprising the wall is equal to
3 100 wt%.

4 The wall in other manufactures, comprises the selectively permeable
5 cellulose ether, ethyl cellulose. The ethyl cellulose comprises an ethoxy
6 group with a degree of substitution, DS, of about 1.4 to 3, equivalent to
7 40% to 50% ethoxy content, and a viscosity range of 7 to 100 centipoise,
8 or higher. More specifically, the wall comprises 40 wt% to 95 wt% ethyl
9 cellulose, from 5 wt% to 60 wt% polyethylene glycol with the total weight
10 percent of all components comprising the wall equal to 100 wt%. In another
11 manufacture the wall comprises 45 wt% to 80 wt% of ethylcellulose, from
12 5 wt% to 30 wt% hydroxypropylcellulose, from 2 wt% to 20 wt% of polyvinyl
13 pyrrolidone, with the total amount of all components comprising the wall equal
14 to 100 wt%.

15

16

EXAMPLE 4

17

18 The antagonist composition according to the above examples wherein
19 the naloxone is replaced by a member selected from the group consisting of
20 naltrexone, nalmeferene, nalide, nalmexone, nalorphine, nalpuphine,
21 nalorphine dinicotinate, and the pharmaceutically acceptable salt.

22

23

EXAMPLE 5

24

25 In the dosage forms provided by the invention, the first composition
26 can comprises 0.1 to 98 wt% opioid base, opioid salt, or opioid derivative;
27 10 to 95 wt% poly(alkylene oxide) possessing a 100,000 to 650,000
28 molecular weight or 10 to 95 wt % of a carboxymethylcellulose, such as
29 sodium carboxymethylcellulose, lithium carboxymethylcellulose, or potassium
30 carboxymethylcellulose possessing a 10,000 to 400,000 molecular weight;

1 1 to 20 wt% poly(vinyl pyrrolidone) of 40,000 to 75,000 molecular weight,
2 or hydroxypropylcellulose or hydroxypropylmethylcellulose; and 0.10 to
3 10 wt% lubricant such as magnesium stearate. In the dosage form,
4 the composition comprising the antagonists comprises 30 to 99 wt%
5 poly(alkylene oxide) exemplified by poly(ethylene oxide) comprising a
6 3,000,000 to 10,000,000 molecular weight, or 20 to 99 wt % of alkali
7 carboxymethylcellulose comprising a 450,000 to 2,500,000 molecular weight
8 available from Aqualon Co., Hopewell, Virginia; 0 to 80 wt% of an osmagent,
9 also known as osmotic effective solute, represented by magnesium sulfate,
10 sodium chloride, sodium bicarbonate, sodium succinate, sodium succinate
11 hexahydrate, lithium chloride, potassium sulfate, sodium sulfate, lithium
12 sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium
13 succinate, tartaric acid, carbohydrates like raffinose, sucrose, glucose,
14 lactose, fructose, sodium chloride, fructose, and potassium chloride dextrose;
15 0.25 to 25 wt% of a hydroxyalkylcellulose selected from the group consisting
16 of hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose,
17 hydroxybutylcellulose, hydroxypropylmethylcellulose,
18 hydroxypropylethylcellulose, hydroxypropylbutylcellulose, which
19 hydroxyalkylcellulose comprises a 7,500 to 75,000 molecular weight;
20 0 to 5 wt% ferric oxide; 0 to 3 wt% antioxidant represented by d-alpha
21 tocopherol, dl-alpha tocopherol, d-alpha tocopherol acetate, dl-alpha-
22 tocopherol acetate, d-alpha tocopherol acid succinate, dl-alpha tocopherol
23 acid succinate, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole,
24 butylated hydroxytoluene, and propyl gallate; 0.50 to 10 wt% of an
25 antagonists, selected from the group consisting of naloxone, naltrexone,
26 nalmeferene, nalide, nalmexone, nalorphine, naluphine, nalorphine dinicotinate,
27 and the pharmaceutically acceptable salts thereof; and 0 to 3 wt% lubricant
28 represented by magnesium stearate, calcium stearate, corn starch, potato
29 starch, bentonite, citrus pulp, and stearic acid; and with all ingredients in the
30 push composition equal to 100 wt%, weight percent.

EXAMPLE 6

The therapeutic compositions manufactured by following the above examples and substituting hydromorphone as the opioid and substituting hydromorphone as the opioid provides a hydromorphone drug composition consisting of 1 to 1000 mg of hydromorphone, hydromorphone base, hydromorphone salt, or hydromorphone derivative; at least one of 25 to 500 mg poly(alkylene oxide) of 100,000 to 750,000 molecular weight, or 25 to 500 mg of an alkali carboxymethylcellulose of 10,000 to 300,000 molecular weight; at least one of 1 to 50 mg of poly(vinylpyrrolidone) of 10,000 to 300,000 molecular weight or 1 to 50 mg of hydroxypropylcellulose or hydroxypropylalkylcellulose of 7,500 to 75,000 molecular weight; 0 to 10 mg of a lubricant such as magnesium stearate; and 0 to 50 mg of a colorant such as ferric oxide.

The dosage form, provided by the example, comprises a push composition that forms a second layer consisting of at least one of 15 to 750 mg of a poly(alkylene oxide) of 3,000,000 to 7,750,000 molecular weight, or 15 to 750 mg of a carboxymethylcellulose such as sodium carboxymethylcellulose, and potassium carboxymethylcellulose of 450,000 to 2,500,000 molecular weight; 0 to 75 mg of an osmagent, also known as osmotically solute represented by magnesium sulfate, sodium chloride, sodium bicarbonate, sodium succinate, sodium succinate hexahydrate, lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates like raffinose, sucrose, glucose, lactose, fructose, sodium chloride, and fructose, potassium chloride and dextrose; 1 to 50 mg of a hydroxyalkylcellulose selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxypropylmethyl-cellulose,

1 hydroxypropylethylcellulose, hydroxypropylbutylcellulose which
2 hydroxyalkylcellulose comprises a 7,500 to 75,000 molecular weight;
3 0 to 10 mg and more preferred 0.05 to 7.5 mg of an antioxidant represented
4 by d-alpha tocopherol acetate, dl-alpha tocopherol, ascorbyl palmitate,
5 butylated hydroxyanidole, butylated hydroxytoluene and propyl gallate;
6 0 to 10 mg of a lubricant represented by magnesium stearate, calcium
7 stearate, corn starch, potato starch, bentonite, citrus pulp, and stearic acid;
8 0 to 10 mg of a colorant; and 0.01 to 20 mg of an antagonist selected from
9 the group consisting of naloxone, naltrexone, nalmeferene, nalide, nalmexone,
10 nalorphine, and naluphine.

11

12

EXAMPLE 7

13

14 The dosage form, further provided by the invention, comprises a push-
15 displacement composition for pushing the hydromorphone composition from
16 the dosage form consisting of at least one of 15 to 500 mg of a poly(alkylene
17 oxide) of 3,000,000 to 10,000,000 molecular weight, or 15 to 750 mg of an
18 alkali carboxymethylcellulose such as sodium carboxymethylcellulose, and
19 potassium carboxymethylcellulose of 450,000 to 2,500,000 molecular weight;
20 0 to 500 mg and more preferred 5 mg to 350 mg of an osmagent, also known
21 as osmotically solute represented by magnesium sulfate, sodium chloride,
22 sodium bicarbonate, sodium succinate, sodium succinate hexahydrate,
23 lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium
24 acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid,
25 carbohydrates like raffinose, sucrose, glucose, lactose, fructose, sodium
26 chloride and fructose, potassium chloride and dextrose; 0.01 to 20 mg of an
27 antagonist for an opioid; 1 to 50 mg of a hydroxyalkylcellulose selected from
28 the group consisting of hydroxyethylcellulose, hydroxypropylcellulose,
29 hydroxyisopropylcellulose, hydroxybutylcellulose,
30 hydroxypropylmethylcellulose, hydroxypropylethylcellulose,

1 hydroxypropylbutylcellulose which hydroxyalkylcellulose comprises a 7,500 to
2 75,000 molecular weight; 0 to 10 mg of an antioxidant represented by d-alpha
3 tocopherol acetate, dl-alpha tocopherol, ascorbyl palmitate, ascorbic acid,
4 butylated hydroxyanidole, butylated hydroxytoluene and propyl gallate;
5 0 to 10 mg of a lubricant represented by magnesium stearate, calcium
6 stearate, corn starch, potato starch, bentonite, citrus pulp, and stearic acid;
7 and 0 to 10 mg of a colorant.

8 9 **EXAMPLE 8**

10
11 The dosage form, as described in Example 2, except no colorant is
12 present in the push composition. Also, rather than two 30 mil exit
13 passageways drilled through the semipermeable wall on the opioid-drug
14 layer, one 30 mil exit passageway is drilled on the opioid-drug layer and one
15 30 mil exit passageway is drilled on the push layer.

16 17 **EXAMPLE 9**

18
19 Same as Example 8, except the poly(ethylene oxide) comprising a
20 5,000,000 to 15,000,000 number-average molecular weight in the push
21 composition.

22 23 **ADDITIONAL DISCLOSURE OF THE INVENTION**

24
25 The expression, "exit means," for the dosage form as used, comprises
26 means and methods suitable for the metered release of beneficial drug
27 morphine from the dosage form. The exit means comprises at least one
28 passageway, orifice, or the like, through the wall for communicating with
29 morphine in the dosage form. The expression, "at least one passageway,"
30 comprises aperture, orifice, bore, micropore, porous composition, porous

1 element through which the drug can migrate, hollow fiber, capillary tube,
2 porous overlay, porous insert, and the like. The expression also includes a
3 material that erodes or is leached from the wall in the fluid environment of use
4 to produce least one passageway in the dosage form. Representative
5 materials suitable for forming at least one passageway, or a multiplicity of
6 passageways, include an erodible poly(glycolic) acid, or poly(lactic) acid
7 member in the wall, a gelatinous filament, poly(vinyl alcohol), leachable
8 materials such as fluid removable pore forming polysaccharides, salts, oxides,
9 or the like. A passageway or a plurality of passageways can be formed by
10 leaching a material such as sorbitol, lactose, fructose, maltose, mannose,
11 glucose, and the like from the wall. The passageway can have any shape
12 such as round, triangular, square, elliptical, and the like, for assisting in the
13 metered release of the opioid-drug from the dosage form. The dosage form
14 can be constructed with one or more passageways in spaced apart relations,
15 or more than one passageway on a single surface of a dosage form.
16 Passageways and equipment for forming passageways are disclosed
17 in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864.
18 Passageways of govern size formed by leaching are disclosed in
19 U.S. Pat. Nos. 4,200,098 and 4,285,987.

20 Exemplary solvents used for the present purpose comprise inorganic
21 and organic solvents that do not adversely harm the materials and the final
22 wall or the final compositions in the dosage form. The solvents broadly
23 include members selected from the group consisting of aqueous solvents,
24 alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated
25 solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures
26 thereof. Typical solvents include acetone, diacetone alcohol, methanol,
27 ethanol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl
28 acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane,
29 ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate,
30 methylene dichloride, ethylene dichloride, propylene dichloride, carbon

1 tetrachloride, chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl
2 ether, isopropyl ether, cyclo-hexane, cyclo-octane, benzene, toluene,
3 naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, aqueous and nonaqueous
4 mixtures thereof, such as acetone and water, acetone and methanol, acetone
5 and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride
6 and methanol.

7 8 DISCLOSURE FOR USING THE INVENTION

9
10 The invention concerns a method for administering an opioid analgesic
11 to a patient, from a dosage form characterized by a separate composition
12 comprising an antagonist for an opioid to substantially lessen opioid abuse.

13 The method provides administering 10 ng to 750 mg of an opioid
14 analgesic to the patient from a dosage form comprising a semipermeable
15 wall permeable to aqueous-biological fluid and impervious to an opioid; an
16 opioid composition, which dosage form comprises 10 to 98 wt% opioid,
17 10 to 80 wt% poly(alkylene oxide) possessing a 100,000 to 650,000
18 molecular weight, and 1 to 20 wt% poly(vinyl pyrrolidone) of 40,000 to
19 75,000 molecular weight, and a push-displacement composition comprising
20 40 to 90 wt% poly(alkylene oxide) comprising a 3,000,000 to 15,000,000
21 molecular weight, 0 to 80 wt% of an osmagent, and 0.25 to 25 wt% of a
22 hydroxyalkylcellulose possessing a 7,500 to 75,000 molecular weight, and
23 0.01 to 10% of an antagonist maintained in the antagonist composition;
24 and 0 to 5% of a colorant which opioid composition and push-displacement
25 compositions are surrounded by the semipermeable wall; and exit means in
26 the wall for delivering the opioid from the dosage form, by imbibing fluid
27 through the wall into the dosage form causing the opioid composition, and
28 causing the push-displacement composition to expand and push the opioid
29 drug composition through the exit means, whereby through the combined

1 operations of the dosage form, the opioid analgesic is delivered at a
2 therapeutically effective dose at a controlled rate over a sustained period
3 of time.

4 The invention is characterized additionally by the invention's ability to
5 administer an opioid analgesic to a patient in need of an opioid analgesic
6 from a dosage form while simultaneously maintaining an opioid antagonist
7 in the dosage form to prevent opioid abuse. Thus, the dosage form of the
8 present invention provides the following advantages: (1) a therapeutic opioid
9 analgesic effect that is essentially constant; (2) smoothness and consistency
10 in the level of opioid analgesic delivered to the blood of the patient;
11 (3) reduced potential for misuse or abuse of the opioid-containing dosage
12 form; (4) maintaining the opioid and antagonist separate in the dosage form;
13 (5) decrease the risk of overdosing and resulting toxic reactions;
14 (6) improvement in patient compliance accompanied by a recommended
15 therapy program; (7) eliminate undesirable interactions and reactions
16 between the opioid and the opioid antagonist contained in the dosage form;
17 (8) administering a drug opioid composition free of an antagonist; and
18 (9) improve the treatment of an opioid addict to correctly and safely use
19 opioid maintenance as both clinical inpatient and clinical outpatient treatment.

20 Inasmuch as the foregoing specification comprises disclosed
21 embodiments, it is understood what variations and modifications may be
22 made herein, in accordance with the principles disclosed, without departing
23 from the invention.

1 We claim:

2

3 1. A dosage form comprising:

4 (1) a wall comprising a semipermeable composition, which wall
5 surrounds:

6 (2) a bilayer core comprising:

7 (a) a first layer comprising an analgesic opioid;

8 (b) a second layer in contact with the first layer,

9 comprising 40 to 99 wt% of a poly(alkylene oxide) possessing a 3,000,000 to
10 10,000,000 number average molecular weight, and 0.25 to 25 wt% of a
11 hydroxyalkylcellulose possessing a number average molecular weight of
12 7,500 to 75,000, and wherein the second layer is characterized by comprising
13 0.75 to 10 wt% of an antagonist selected from the group consisting of
14 naltrexone, naloxone, nalmefene, nalide, nalmexone, nalorphine, and
15 naluphine; and,

16 (3) an exit in the wall for releasing the opioid analgesic from the
17 dosage form.

18 2. The dosage form according to claim 1, wherein the antagonist is
19 present as the pharmaceutically acceptable salt.

20 3. The dosage form according to claim 1 wherein the second layer
21 comprises an osmagent.

22 4. The dosage form according to claim 1, wherein the analgesic opioid
23 comprises a member selected from the group consisting of apomorphine,
24 apocodeine, codeine, dihydrocodeine, dihydromorphine, hydrocodone,
25 hydroxymethylmorphian, hydromorphone, methylnorphine, morphine,
26 normorphine, oxycodone, benzylmorphine, and oxymorphone.

27 5. The dosage form according to claim 1, wherein the analgesic opioid
28 comprises a member selected from the group consisting of alfentanil,
29 fentanyl, lofentanil, and sufentanil.

- 1 6. The dosage form according to claim 1 wherein the second layer
2 comprises an antioxidant.
- 3 7. The dosage form according to claim 1, wherein the first layer
4 comprises a member selected from the group consisting of allylprodine,
5 alphaprodine, anileridine, bezitramide, buprenorphine, butophanol,
6 clonitazene, cyclorphan, cyprenorphine, desomorphine, dextromoramide,
7 dezocine, diampromide, diminoxadol, eptazocine, ethylmorphine,
8 hydroxypethidine, levophenacymorphan, levorphanol, neomorphine,
9 normethadone, pholcodine, and profadol, and wherein the first layer
10 composition is free of antagonist.
- 11 8. A dosage form comprising:
- 12 (1) a wall comprising a semipermeable composition, which wall
13 surrounds:
- 14 (2) a bilayer core comprising:
- 15 (a) a first layer comprising an analgesic opioid;
- 16 (b) a second layer in contact with the first layer comprising 20 to
17 99 wt% of a poly(carboxymethylcellulose) comprising a 450,000 to 2,500,000
18 number average molecular weight, and 0.25 to 25 wt% of a
19 hydroxyalkylcellulose possessing a number average molecular weight of
20 7,500 to 75,000. and wherein the second layer is characterized by comprising
21 0.75 to 10 wt% of an antagonist selected from the group consisting of
22 naltrexone, naloxone, nalmeferine, nalide, nalmexone, nalorphine, and
23 naluphine; and,
- 24 (3) an exit passageway in the wall for releasing the opioid analgesic
25 from the dosage form.
- 26 9. The dosage form according to claim 8, wherein the antagonist is
27 present as the pharmaceutically acceptable salt.

1 10. The dosage form according to claim 8, wherein the analgesic
2 opioid comprises a member selected from the group consisting of
3 apomorphine, apocodeine, codeine, dihydrocodeine, dihydromorphine,
4 hydrocodone, hydroxymethylmorphane, hydromorphone, methylmorphine,
5 morphine, normorphine, oxycodone, benzylmorphine, and oxymorphone.

6 11. The dosage form according to claim 8, wherein the analgesic
7 opioid comprises a member selected from the group consisting of alfentanil,
8 fentanyl, lofentanil, and sufentanil.

9 12. The dosage form according to claim 8, wherein the first layer is a
10 composition comprising a member selected from the group consisting of
11 allylprodine, alphaprodine, anileridine, bezitramide, buprenorphine,
12 butorphanol, clonitazene, cyclorphan, cyprenorphine, desmorphine,
13 dextromoramide, dezocine, diampromide, diminoxadol, eptazocine,
14 ethylmorphine, hydroxypethidine, levorphenacylmorphane, levorphanol,
15 neomorphine, normethadone, pholcodine, and profadol, and wherein the
16 first layer composition is free of antagonist and pressed as a tablet.

17 13. The dosage form according to claim 8 wherein the dosage form
18 comprises a member selected from the group consisting of d-alpha
19 tocopherol acetate, dl-alpha tocopherol, ascorbyl palmitate, ascorbic acid,
20 butylated hydroxyanisole, butylated hydroxytoluene, and propylgallate.

21 14. A composition of matter comprising 10 ng to 275 mg of naloxone
22 and 15 mg to 750 mg of a poly(alkylene oxide) comprising a 3,000,000 to
23 10,000,000 molecular weight.

24 15. The composition of matter according to claim 14, wherein the
25 naloxone is replaced by a member selected from the group consisting of
26 naltrexone, nalbuphine, nalbuphine, nalmexone, nalorphine, and nalbuphine, and
27 the composition is compressed into a tablet.

28 16. A composition of matter comprising 10 ng to 275 mg of naloxone
29 and 15 to 750 mg of a poly(carboxymethylcellulose) comprising a 450,000 to
30 2,500,000 molecular weight.

1 17. The composition of matter according to claim 16, wherein the
2 naloxone is replaced by a member selected from the group consisting of
3 naltrexone, nalmefene, nalide, nalmexane, nalorphine, and nalpuphine and
4 the composition is compressed into a tablet.

5 18. A composition of matter comprising 10 ng to 275 mg of
6 naloxone, 15 mg to 750 mg of a poly(alkylene oxide) comprising a 3,000,000
7 to 10,000,000 molecular weight, 5 mg to 350 mg of an osmagent, and
8 0.05 mg to 7.5 mg of an antioxidant.

9 19. A composite of matter comprising 10 ng to 275 mg of naloxone,
10 15 mg to 750 mg of a poly(carboxymethylcellulose) comprising a 450,000 to
11 2,500,000 molecular weight, 5 mg to 350 mg of an osmagent and 0.05 mg to
12 7.5 mg of an antioxidant.